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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,251	06/06/2002	Keizo Inoue	04853.0089	7644

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

84.

Office Action Summary	Application No.	Applicant(s)	
	10/069,251	INOUE ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. 04/04.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Amendment

Applicant's amendment filed 12/22/2003 has been entered. Claims 27-34 have been amended. Claims 35 and 36 have been added. Claims 27-36 are pending and under consideration in the instant action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous transgenic mouse whose genome comprises a homozygous disruption of the endogenous α-TTP gene wherein the mouse exhibits non-detectable levels of vitamin E or wherein the mouse, when female, exhibits a failure to maintain pregnancy, does not reasonably provide enablement for all other mice embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The rejection is maintained for the reasons set forth on pages 2-4 of the previous office action mailed 07/01/2003.

Applicant's arguments have been fully considered and are not considered persuasive. Applicant argues that the heterozygous and chimeric mice encompassed by claims 27,29,31,33 and newly added claim 35 are fully enabled because the claims recite a genotype that is enabled (page 6, paragraph 2). Applicant argues further that the phenotypic limitation recited for the

homozygous mouse limits the phenotype of the chimeric and heterozygous mice encompassed by the claims (page 7, lines 4-7). Applicant also argues that the specification enables making both chimeric and heterozygous mice and that said mice can be used as intermediates to make a homozygous mouse exhibiting a vitamin E deficiency phenotype (page 8 and page 9, last paragraph). Applicant cites Reiners v. Mehltretter in stating that products are useful if they serve as starting materials or intermediates for producing other materials that are useful. Applicant asserts that the claimed chimeric and heterozygous mice are intermediates that are useful for producing the claimed homozygous mouse exhibiting non-detectable levels of vitamin E.

In response, it is maintained that the claims are not fully enabled by recitation of a genotype. The specification teaches creation of chimeric and transgenic mice comprising a heterozygous disruption of the α-TTP gene, however, the specification fails to teach that these mice have a phenotype so as to provide a use for the mouse. The phenotypic limitation of the homozygous mouse fails limit the phenotype for the heterozygous and chimeric mice encompassed by the claims. Therefore, the claims, as written, encompass chimeric and heterozygous mice exhibiting any phenotype, including a wild-type phenotype. The specification does not teach how to use the claimed mice exhibiting a wild-type phenotype. With respect to Reiners v. Mehltretter as it relates to use of the claimed heterozygotes and chimeric mice as intermediates, Applicants argue that the phenotypically wild-type chimeric and heterozygous mice encompassed by the claims can be used as intermediates to generate homozygous mice that exhibit non-detectable levels of vitamin E. Reiners v. Mehltretter is drawn to chemical intermediates being useful in generating a chemical product, not a transgenic animal. A chemical intermediate is well-defined product. The chimeric and heterozygous mice encompassed by the

claims are not well-defined and, as claimed, can include mice exhibiting any phenotype, including wildtype. The well-defined chemical intermediates of Reiners v. Mehltretter do not apply to the heterozygous and chimeric mice of the instant invention as broadly claimed. Therefore, specification does not enable one of skill in the art to use the chimeric and heterozygous mice encompassed by the claims.

Applicant notes that the phenotypic limitations of claim 29 do not apply to the claimed heterozygous mice (page 9, second paragraph).

In response, Applicant's argument is noted, however, it is maintained that the claim encompasses heterozygous and chimeric mice exhibiting a wild-type phenotype and the claim remains rejected for the reasons set forth above.

The specification also fails to enable making a genetically modified mouse comprising a disruption in the α-TTP gene wherein the mouse exhibits any vitamin E deficiency phenotype. The specification teaches that female mice whose somatic and germ cells comprise a homozygous disruption of the α-TTP gene exhibit a failure to maintain pregnancy as assayed by the fetal resorption test (pages 20-21, Example 6). The specification does not teach any phenotype for homozygous male mice other than non-detectable levels of vitamin E. The state of the art at the time of filing was that there were several phenotypic effects of a vitamin E deficiency including ataxia (Cavalier, 1998, Am J Hum Genet, Vol. 62, pages 301-310) and myopathy (Thomas, 1993, J Anat, Vol. 183, pages 451-461). Therefore, the specification fails to provide the guidance necessary to generate a genetically modified mouse comprising a disruption in the α-TTP gene wherein the mouse exhibits any vitamin E deficiency phenotype other than non-detectable levels of vitamin E and failure of female mice to maintain pregnancy.

The claims are directed to a genetically modified mouse and encompass any type of genetic modification, including those that do not require a transgene such as ENU or EMS mutagenesis. The claims also encompass a naturally occurring mutation in the α-TTP gene as the claim fails to correlate the genetic modification to the knockout of the α-TTP gene. The specification teaches a transgenic mouse wherein a transgene replaces exon 1 of the α-TTP gene, resulting in a disruption of normal α-TTP gene expression, wherein no α-TTP is expressed. The specification does not teach any non-transgenic form of genetic modification as claimed. Due to the lack of guidance provided by the specification with respect to how to genetically modify the α-TTP gene in a mouse using any means other than transgene insertion into the endogenous α-TTP gene, it would require undue experimentation to generate the genetically modified mice that are broadly encompassed by the claims. Replacing the phrase "genetically modified" with "transgenic" in claims 27-36 and correlating a disruption of the α-TTP gene to the transgene would overcome this rejection.

Claims 27-36 encompass mice that comprise an exogenously inserted knockout allele of the α-TTP gene wherein said α-TTP gene is not the endogenous α-TTP gene. The specification teaches using homologous recombination to generate an insertional disruption in the endogenous α-TTP gene. The specification does not teach inserting a transgene comprising a knockout allele into the genome of a mouse. It would require undue experimentation for one of skill in the art at the time of filing to generate a transgenic mouse whose genome comprises a transgene comprising a knockout allele of the α-TTP gene wherein the knockout allele does not affect the endogenous α-TTP gene and wherein the mouse exhibits a vitamin E deficiency. Replacing the phrase "whose somatic and germline cells are homozygous for a knockout allele of the genomic

α-TTP gene" with "whose genome comprises a homozygous for a disruption of the endogenous α-TTP gene" would overcome this rejection.

Claims 27-36 encompass mice comprising a knockout allele of the α-TTP gene wherein expression from the knockout allele is partially inhibited. The specification defines "inhibited" as encompassing both complete and partial inhibition (page 4, paragraph 2). The specification is not enabling for partially inhibiting expression of the α-TTP gene. The specification teaches making a knockout mutation in the α-TTP gene by replacing the first exon of the α-TTP gene with the neomycin resistance gene (page 10, paragraph 3). In doing so, expression of α-TTP gene is prevented by the loss of the α-TTP translational start codon, presence of the neomycin resistance gene stop codon and loss of at least the amino terminus of the α-TTP protein if translation can be initiated downstream of the replaced first exon. The specification does not teach how to make a knockout such that partial inhibition of a gene occurs. A knockout allele is defined as one with no resulting functional gene product. Drug Discovery and Development defines the term "knockout" as "An alteration of a gene that results in loss of function; a transgenic organism in which a gene has been inactivated" (http://www.dddmag.com/Glossary.aspx?RPTID=KWSRCH&SEARCHMETHOD=WORD&SEARCHWORD=Knockout). Therefore, partial inhibition would not fit under this definition. Furthermore, the specification teaches replacement of exon 1 of the gene, resulting in no functional gene product as evidenced by the severe vitamin E deficiency. The specification does not teach how to genetically alter the endogenous α-TTP gene such that expression is reduced. The specification does not teach which regions or residues within the coding region of the gene can result in a reduction of gene expression when mutated. The specification does not give any

guidance whatsoever as to the location of any gene regulatory regions that might be a mutational target to decrease α-TTP gene expression. Furthermore, the specification fails to provide any guidance as to how much of an inhibition of α-TTP gene expression would be required to cause the claimed phenotypes. Therefore, provided the lack of guidance in the specification with respect to how to alter the endogenous α-TTP gene such that reduced levels of expression results and what those levels might be such that the claimed phenotype is attained, it would require undue experimentation to determine how to generate the claimed mice wherein α-TTP gene expression is inhibited in any manner other than total inhibition as claimed.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "knockout allele" in claims 27-36 is used by the claim to mean "hypomorphic allele" or "allele

with reduced expression", while the accepted meaning is "null allele." The term is indefinite because the specification does not clearly redefine the term.

Allowable Subject Matter

The following claim is drafted by the examiner and presented to applicant for consideration:

A transgenic mouse whose genome comprises a homozygous disruption of the endogenous α-TTP gene wherein α-TTP is not expressed and said transgenic mouse exhibits non-detectable levels of vitamin E.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Fri 6:00-2:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

PETER PARAS, JR.
PRIMARY EXAMINER

Valarie Bertoglio
Examiner
Art Unit 1632